

REMARKS

Claims 36, 37, 41, 42, 44, 45 and 49-66 have been canceled without prejudice and claims 35, 40, 43, and 48 have been amended. Support for these amendments can be found throughout the claims and specification as filed. Specifically, support may be found in the specification at page 3, line 27; at page 4, lines 4-10 and 14-15; at page 6, lines 20-22; at page 11, line 35 through page 12, line 26; at page 16, lines 14-23; at page 26, lines 10-24; at page 28, line 28 through page 29, line 9; at page 46, lines 3-16; at page 47, lines 22-30; at page 48, line 24 through page 49, line 14; and at page 79, lines 11-17. No new matter has been added by way of amendment. Accordingly, claims 35, 38-40, 43, and 46-48 will be pending upon entry of this amendment.

Information Disclosure Statement

The Examiner objected to the Information Disclosure Statement submitted September 27, 2002 because copies of the references A1-A16 and B1-B6 were missing. Applicants submit herewith a Supplemental Information Disclosure Statement with paper copies of the references being cited therein. Entry and consideration of the information cited in the enclosed Supplemental Information Disclosure Statement is respectfully requested.

Drawings

The Examiner rejected Figures 1A and 1B as being unnecessarily redundant with the sequence listing. The Examiner requested amendment of the specification to delete any Figures (e.g. Figures 1A and 1B) which consist only of nucleic acid or protein sequences which have been submitted in their entirety in computer readable format, in addition to amendment of the specification to reflect replacement of the Figure by the appropriate SEQ ID NO. Applicants submit herewith amended formal Figures, in which Figures 1A and 1B have been deleted and remaining Figures 2-8B renumbered as 1-7B. Applicants further submit that amendments to the specification have been made to correctly reflect the deletion of Figures 1A and 1B, as well as proper reference to remaining Figures. Replacement sheets for the amended formal Figures 1-7B are attached as Appendix A, and annotated sheets showing changes are attached as Appendix B.

Specification

The Examiner objected to the specification because of the following informality: "at page 79, line 17, the Specification states 'The results of these analyses are set forth in Figures 5-7'. However, the Examiner believes that it should read 'Figures 6-8'."

Applicants submit that in view of the amendments to the Drawings above (i.e. deletion of Figures 1A and 1B and renumbering of Figures 2-8B) the objection to the specification is moot, since the Figures containing the results of the expression analyses are now numbered Figures 5-7. Reconsideration and withdrawal of this objection is respectfully requested.

Claim Objections

The Examiner has objected to claims 40, 48, 56, and 64 "because of the following informalities: Claims 40, 48, 56, and 64 encompass non-elected inventions, e.g., part (d) a yeast two-hybrid assay, and part (e) an assay for lipid metabolism." Applicants have amended claims 40 and 48 to remove parts (d) and (e) which refer to a yeast two-hybrid assay and an assay for lipid metabolism, respectively. In addition, claims 56 and 64 have been canceled. Applicants submit that the objection to claims 40, 48, 56, and 64 is thus rendered moot, and respectfully request reconsideration and withdrawal of this objection.

The Rejection of Claims 35-66 Under 35 USC §112, Second Paragraph Should Be Withdrawn

Claims 35-66 were rejected by the Examiner under 35 USC §112, Second Paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The Examiner rejected claims 35, 43, 51, and 59 as being unclear in what is meant by the terms "pain disorder" and "pain signaling mechanism".

Applicants have amended claims 35 and 43, removing the phrases "pain disorder" and "pain signaling mechanism". In addition, claims 51 and 59 have been canceled. Applicants submit that the foregoing amendments to the claims thus render the rejection of claims 35-66 under 35 USC §112, Second Paragraph, moot. Applicants respectfully request reconsideration and withdrawal of the rejection.

**The Rejection of Claims 35-66 Under 35 USC §112, First Paragraph (Enablement)
Should Be Withdrawn**

Claims 35-66 were rejected by the Examiner under 35 USC §112, First Paragraph as failing to comply with the enablement requirement. Specifically, the Examiner rejected the claims drawn to a method of identifying candidate compounds for modulating a pain response, arguing that the specification as filed does not provide guidance or examples that would enable a skilled artisan to use the disclosed methods of identifying candidate compounds for modulating a pain response or modulating a pain signaling mechanism.

Applicants have amended claims 35 and 43, removing the phrases “pain disorder” and “pain signaling mechanism”. In addition, claims 51 and 59 have been canceled. Applicants submit that the foregoing amendments to the claims thus render the rejection of claims 35-66 under 35 USC §112, First Paragraph (enablement), moot. It is believed that the foregoing amendments also render the specification enabling for the claimed methods as amended. Applicants respectfully request reconsideration and withdrawal of the rejection.

**The Rejection of Claims 35-36, 38-44, 46-52, 54-60 and 62-66 Under 35 USC §102 Should Be
Withdrawn**

Claims 35-36, 38-44, 46-52, 54-60 and 62-66 were rejected by the Examiner under 35 USC §102(e) as being anticipated by Baughn et al (WO 02/12467 A2, priority date 4 August 2000, citation #BA on IDS filed 07 September 2004). Specifically, the Examiner states that “Baughn et al teach a DME 10 polypeptide (SEQ ID NO:10) that has 100% sequence identity to SEQ ID NO:2 of the instant application...that they disclose as a carboxylesterase.” The Examiner additionally states that “Baughn et al also teach that the DME 10 polypeptide may be used to screen for compounds...that bind DME 10”.

Applicants respectfully traverse the rejection and submit that Baughn et al do not teach each and every element of the newly pending claims. Specifically, Applicants have amended independent claims 35 and 43 to specify that the methods be carried out in specific cell types, namely “a brain cell, a cell derived from spinal cord, and a cell derived from dorsal root ganglion.” Applicants submit that Baughn et al. do not teach such methods and therefore do not teach each and every element of the newly pending claims. Applicants submit that the foregoing amendments to claims 35 and 43, and cancellation of claims 36, 41, 42, 44 and 49-66 thus render the rejection of claims 35-36, 38-44, 46-52, 54-60 and 62-66 under 35 USC §102(e) moot. Applicants respectfully request reconsideration and withdrawal of the rejection.

CONCLUSIONS

In view of the amendments and remarks herein, Applicants respectfully submit that the objections and rejections presented by the Examiner are now overcome and that this application is in condition for allowance. If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned.

This paper is being filed timely as a request for a one month extension of time is filed concurrently herewith. No additional extensions of time are required. In the event any additional extensions of time are necessary, the undersigned hereby authorizes the requisite fees to be charged to Deposit Account No. 501668.

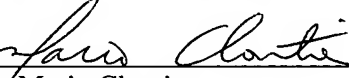
Entry of the remarks made herein is respectfully requested.

March 15, 2005

Respectfully submitted,

MILLENNIUM PHARMACEUTICALS, INC.

By



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Limited Recognition under 37 CFR §11.9(b)

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IN THE DRAWINGS:

Applicants submit herewith amended formal figures to address the issues raised by the Examiner. For the Examiner's convenience, Applicants submit herewith: A) replacement sheets containing the amended formal figures (APPENDIX A); and B) annotated sheets showing the changes made to the figures (APPENDIX B).

As requested by the Examiner, Figure 1 has been deleted and Figures 2-8B have been renumbered as Figures 1-7B. The replacement sheets in Appendix A, which include the renumbered Figures 1-7B, replaces the original sheets including Fig. 1-8B.



Patitioner's Docket No. MPI00-408P1RM

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:	Kapeller-Libermann, Rosana, et al.		
Application No.:	10/001,227	Group No.:	1647
Filed:	November 30, 2001	Examiner:	Lockard, Jon McClelland
For:	METHODS OF USING 18903 TO TREAT PAIN AND PAIN-RELATED DISORDERS		

**Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450**

Appendix A: Replacement Drawings

(Figures 1, 2A-2C, 3A-3D, 4A-4C, 5A-5B, 6A-6B, 7A-1-7A-5, 7B)



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Appendix B

(Annotated Sheets with changes marked)



ANNOTATED SHEET

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FIG. 1A

Input file Fbh18903FL.seq; Output File 18903.trans
Sequence length 1983

CCTTTAGCCAATTGGCCGAGGCTCCCGCCAGTACTTGCTGGCAGGATTAAAGACAGATAAAAGTGTGCTCACAG
M P S T V L P S T V L P S L L 15
ACTGTAGACACGGCTACC ATG CCA TCC ACA GTG TTG CCA TCC ACA GTG TTG CCA TCA CTC CTG 45
P T A G A G W S M R W I L C W S L T L C 35
CCC ACA GCA GGA GCT GGC TGG AGC ATG AGG TGG ATT CTG TGC TGG AGC CTC ACC CTC TGC 105
L M A Q T A L G A L H T K R P Q V V T K 55
CTG ATG GCG CAG ACG GCC TTG GGT GCC TTG CAC ACC AAG AGG CCT CAA GTG GTC ACC AAA 165
Y G T L Q G K Q M H V G K T P I Q V F L 75
TAT GGA ACC CTG CAA GGA AAA CAG ATG CAT GTG GGG AAG ACA CCC ATC CAA GTG TTT TTA 225
G V P F S R P P L G I L R F A P P E P P 95
GGA GTC CCC TTC TCC AGA CCT CCT CTA GGT ATC CTC AGG TTT GCA CCT CCA GAA CCC CCG 285
E P W K G I R D A T T Y P P G C L Q E S 115
GAG CCC TGG AAA GGA ATC AGA GAT GCT ACC ACC TAC CCG CCT GGG TGC CTG CAG GAG TCC 345
W G Q L A S M Y V S T R E R Y K W L R F 135
TGG GGC CAG CTG GCC TGG ATG TAC GTC AGC ACG CGG GAA CGG TAC AAG TGG CTG CGC TTC 405
S E D C L Y L N V Y A P A R A P G D P Q 155
AGC GAG GAC TGT CTG TAC CTG AAC GTG TAC GCG CCG GCG CGC GCG CCC GGG GAT CCC CAG 465
L P V M V W F P G G A F I V G A A S S Y 175
~~CTG CCA GTG ATG GTC TGG TTG GCG GGA GGC TTG ATG GTC GGC GGT TCT TCG TAC 525~~



FIG. 1B

E	G	S	D	L	A	A	R	E	K	V	V	L	V	F	L	Q	H	R	L	195
GAG	GGC	TCT	GAC	TTG	GCC	GCC	CGC	GAG	AAA	GTG	GTG	CTG	GTG	TTT	CTG	CAG	CAC	AGG	CTC	585
G	I	F	G	F	L	S	T	D	D	S	H	A	R	G	N	W	G	L	L	215
GGC	ATC	TTC	GGC	TTC	CTG	AGC	ACG	GAC	GAC	AGC	CAC	GCG	CGC	GGG	AAC	TGG	GGG	CTG	CTG	645
D	Q	M	A	A	L	R	W	V	Q	E	N	I	A	A	F	G	Q	D	P	235
GAC	CAG	ATG	GCG	GCT	CTG	CGC	TGG	GTG	CAG	GAG	AAC	ATC	GCA	GCC	TTC	GGG	GGA	GAC	CCA	705
G	N	V	T	L	F	G	Q	S	A	G	A	M	S	I	S	G	L	M	M	255
GGA	AAT	GTG	ACC	CTG	TTC	GGC	CAG	TCG	GCG	GGG	GCC	ATG	AGC	ATC	TCA	GGA	CTG	ATG	ATG	765
S	P	L	A	S	G	L	F	H	R	A	I	S	Q	S	G	T	A	L	F	275
TCA	CCC	CTA	GCC	TCG	GGT	CTC	TTC	CAT	CGG	GCC	ATT	TCC	CAG	AGT	GGC	ACC	GCG	TTA	TTC	825
R	L	F	I	T	S	N	P	L	K	V	K	K	K	V	A	H	L	A	G	295
AGA	CTT	TTC	ATC	ACT	AGT	AAC	CCA	CTG	AAA	GTG	GCC	AAG	AAG	GTT	GCC	CAC	CTG	GCT	GGA	885
C	N	H	N	S	T	Q	I	L	V	N	C	L	R	A	L	S	G	T	K	315
TGC	AAC	CAC	AAC	AGC	ACA	CAG	ATC	CTG	GTA	AAC	TGC	CTG	AGG	GCA	CTA	TCA	GGG	ACC	AAG	945
V	M	R	V	S	N	K	M	R	F	L	Q	L	N	F	Q	R	D	P	E	335
GTG	ATG	CGT	GTG	TCC	AAC	AAG	ATG	AGA	TTC	CTC	CAA	CTG	AAC	TTC	CAG	AGA	GAC	CCG	GAA	1005
E	I	I	W	S	M	S	P	V	V	D	G	V	V	I	P	D	D	P	L	355
GAG	ATT	ATC	TGG	TCC	ATG	AGC	CCT	GTG	GTG	GAT	GGT	GTG	GTG	ATC	CCA	GAT	GAC	CCT	TTG	1065
V	L	L	T	Q	G	K	V	S	S	V	P	Y	L	L	G	V	N	N	L	375
GTG	CTC	CTG	ACC	CAG	GGG	AAG	GTT	TCA	TCT	GTG	CCC	TAC	CTT	CTA	GGT	GTC	AAC	AAC	CTG	1125
E	F	N	W	L	L	P	Y	I	M	K	F	P	L	N	R	Q	A	M	R	395
GAA	TTC	AAT	TGG	CTG	TTG	CCT	TAT	ATG	ATG	ATG	TTC	CCG	CTA	AAC	CGG	CAG	GCG	ATG	AGA	1185



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FIG. 1C

K E T I T K M L W S T R T L L N I T K E 415
AAG GAA ACC ATC ACT AAG ATG CTC TGG AGT ACC CGC ACC CTG TTG AAT ATC ACC AAG GAG 1245

Q V P L V V E E Y L D N V N E H D W K M 435
CAG GTA CCA CTT GTG GTG GAG TAC CTG GAC AAT GTC AAT GAG CAT GAC TGG AAG ATG 1305

L R N R M M D I V Q D A T F V Y A T L Q 455
CTA CGA AAC CGT ATG ATG GAC ATA GTT CAA GAT GCC ACT TTC GTG TAT GCC ACA CTG CAG 1365

T A H Y H R D A G L P V Y L Y E F E H H 475
ACT GCT CAC TAC CAC GAT GCC GGC CTC CCT GTC TAC CTG TAT GAA TTT GAG CAC CAC 1425

A R G I I V K P R T D G A D H G D E M Y 495
GCT CGT GGA ATA ATC GTC AAA CCC CGC ACT GAT GGG SCA GAC CAT GGG GAT GAG ATG TAC 1485

F L F G G P F A T G L S M G K E K A L S 515
TTC CTC TTT GGG GGC CCC TTC GCC ACA GGC CTT TCC ATG GGT AAG GAG AAG GCA CTT AGC 1545

L Q M M K Y W A N F A R T G N P N D G N 535
CTC CAG ATG ATG AAA TAC TGG GCC AAC TTT GCC CGC ACA GGA AAC CCC AAT GAT GGG AAT 1605

L P C W P R Y N K D E K Y L Q L D F T T 555
CTG CCC TGC TGG CCA CGC TAC AAC AAG GAT GAA AAG TAC CTG CAG CTG GAT TTT ACC ACA 1665

R V G M K L K E K K M A F W M S L Y Q S 575
AGA GTG GGC ATG AAG CTC AAG GAG AAG AAG ATG GCT TTT TGG ATG AGT CTG TAC CAG TCT 1725

Q R P E K Q R Q F * 585
CAA AGA CCT GAG AAG CAG AGG CAA TTC TAA 1755

GGGTGCTATGCAGGAAGGAGCCAAAGAGGGGTTTGCCCCCACCATCCAGGCCCTGGGGAGACTAGCCATGGACATACC

GGGGAGAGAGTCTACCCAGGGCCGAATTCCCTTTAAACCTCCAGGACTAG

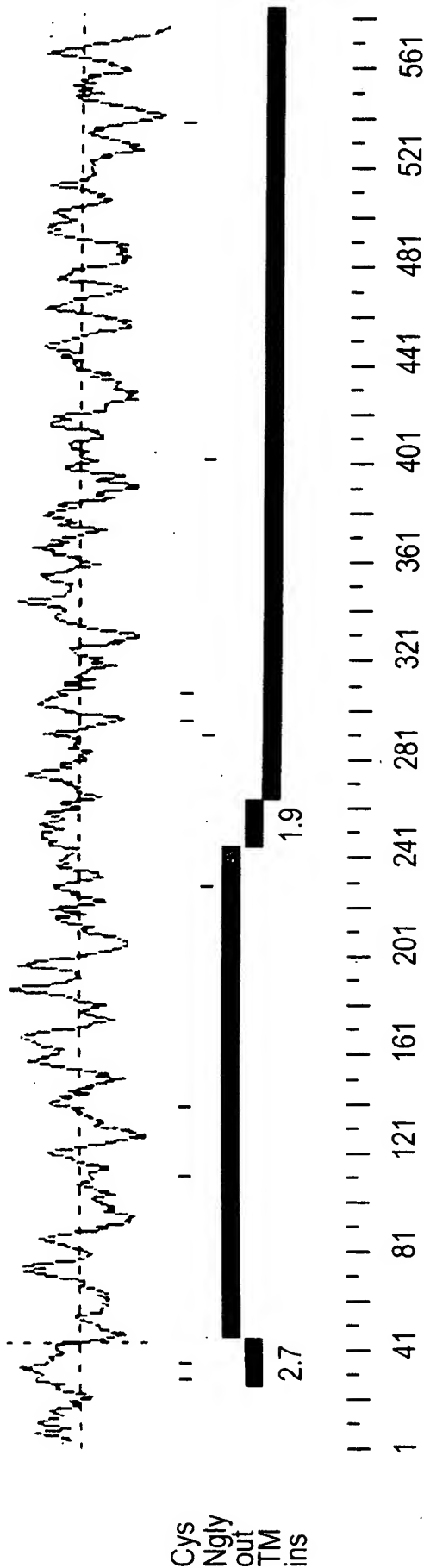


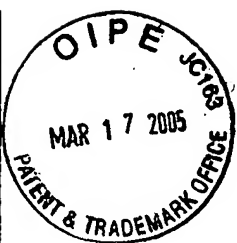
ANNOTATED SHEET
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FIG. 1
~~FIG. 2~~

PFAM

no HMM hits
COesterase





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FIG. 2A
~~FIG. 3A~~

Protein Family / Domain Matches, HMMer version 2

Searching for complete domains in PFAM
hmmpfam - search a single seq against HMM database
HMMER 2.1.1 (Dec 1998)
Copyright (C) 1992-1998 Washington University School of Medicine
HMMER is freely distributed under the GNU General Public License (GPL).

HMM file: /prod/ddm/seqanal/pfam/pfam6.4/pfam
Sequence file: /prod/ddm/wspace/orfanal/oa-script.6214.seq
Query: Fbh18903FL

Scores for sequence family classification (score includes all domains):
Model Description Score E-value N

COesterase Carboxylesterase 558.6 4.1e-164 1

Parsed for domains:
Model Domain seq-f seq-t hmm-f hmm-t score E-value

COesterase 1/1 25 569 .. 1 612 [] 558.6 4.1e-164

Alignments of top-scoring domains:
COesterase: domain 1 of 1, from 25 to 569: score 558.6, E = 4.1e-164
*->mvllllfllllllliavlaaakaspdp1lVatnnVlcGkvrGvnek
+l+ +L 1 1 ++ +l+a+++ ++ V t++ G++ G++
18903 25 RWILCWSLTLCIMAQTAIGALHT---KRPQVVTKY---GTIQGKQMH 65

tdngeqsvysFLGIPYAePPVGnLRFkaPqPYkepWsdvldatkyppsCl
+ ++ +FLG+P+ PP+G LRF +P+P +epW++++dAt+ypp Cl
18903 66 VGKT--PIQVFLGVFSPPLGILRFAPPEP-PEPWKIGIRDATTYPPGCL 112



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FIG. 2B

~~FIG. 3B~~

18903 113 QdddfgslsdlKvalkmlslgwnklvg...lklSEDCLYLNvytpknt
Q + +g+ 1 +++ ++ + + 1 +sEDCLYLNvy P+ +
Q-ESWGQ-----LASMYVSTREYkwlRfSEdCLYLNvyAPARA 150

18903 151 kpsklPVMvWihGGGFmFGsgshslplslYdgeslaregnVivVsiNYRL
+ + +lPVMvW +GG+F +G++ s+Y g+ la++++V++V ++ RL
PGDPQLPVMVWFPGGAFIVGAA-----SSYEGSDLAAREKVVLVFLQHRL 195

18903 196 GplGLstgddklpgsGNyGLLDQrIALkKWVqNIaaFGGDPnsVTifGe
G++GFLst+d+++ GN+GLLDQ +AL+WVq+NiaaFGGDP++VT+fG+
GIFGFLSTDDSHAR--GNWGLLDQMAALRWQENIAAFGGDPGNVTLFGQ 243

18903 244 SAGaaSVsllllsngGDNppsskgLFhRAIsqSGsalspwaiesnarg
SAGa+S+s l++s p++ gLFhRAIsqSG+al +i+s+ +
SAGAMSISGLMMS-----PLA-SGLFHRAIsqSGTALFRlFITSNP--LK 285

18903 286 rakelarllGCnetsssellldCLRsksaeelLeatrsflfeyvpflplf
ak++a l+GCn++s l+ CLR s + + + + + f + +f +
VAKKVAHLAGCNHNSTQILVNCILRALSGTKVMRVSNK-MRFLQLNFQRDP 334

18903 335 l....aFgPvvDGdDapeafipedPeelikeckfadvPyliGvtdEGgy
++ + +PvvDG+ +ip+dP+ l+ +Gk + vPyl Gv++ E+ +
EeiiwSMSPPVVDGV-----VIPDDPLVLLTQGVSSVPYLLGVNNLEFNW 379

18903 380 faamllnasskgedelkktetnpdvlellkyllyfayasealnikdmddlad
++++ +++ + + ket ++ l+ ll+ + +
LLPYIMKFPPLNR-QAMRKETITK-MLWSTRTLLN-ITKEQ-----VP 418

18903 419 kvlekYpgdvddfsvesrkpnldmltdllFkcptrvaadlhakhggsPv
v e+Y++ v + + ++ + d++ D +F+++ + ++ +++g Pv
LVVEEYLDNVNEHDWKMLNRMMDIVQDATFVYA-TLQTAHYHRDAGLPV 467



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FIG. 2C

FIG. 3C

18903 468 YLYEFEHHAR-----GIIVKPRTDGADHGDEMYFLFGGPFATG-LS-- 507
YaYvfdhpasfgigQflakrvdpefggavHgdEiffvFgnpllkeqlyka
Y+Y+f h+a+ + v+p+++ga+HgdE++f+Fg p+ ++ 1
teeeeksssktmmywanFAktGnPnngtsnglvvWpkytseeqkYslli
e++s +mm+ywanFA+tGnP n++ +l+ Wp y+++e +l+
18903 508 MGKEKALS-LQMMKYWANFARTGNP-NDG--NLPCWPRYNKDEK--YLQL 551
llttitaqklkardprkvlcnfw<-*
+tt +klk+++ ++fw
18903 552 DFTTRVGMKLKEKK-----MAFW 569

//

Searching for complete domains in SMART



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~~FIG. 4A~~

GAP of: FrGcgManager_76_IOA81nWg_ check: 5132 from: 1 to: 1983

Fbh18903FL - Import - vector trimmed

to: FrGcgManager_76_JOA3WXZ1_ check: 1319 from: 1 to: 2456

z34105 in Patent Nucleotide

Symbol comparison table: /ddm_local/gcg/gcg_9.1/

1/gcgcore/data/rundata/nwsgapdna.cmp

CompCheck: 8760

Gap Weight:	12	Average Match:	10.000
Length Weight:	4	Average Mismatch:	0.000
Quality:	13796	Length:	2746
Ratio:	6.957	Gaps:	14
Percent Similarity:	92.617	Percent Identity:	92.617

Match display thresholds for the alignment(s):

| = IDENTITY

: = 5

. = 1

FrGcgManager_76_IOA81nWg_ x FrGcgManager_76_JOA3WXZ1

..

```
COE-2      1 .....CCT 3
Z34105 101 CATTTCGCCTTGCTGACGGCGTCGAGCCCTGGCCAGACATGTCCACAGGG 150
          4 TTAGCCAATTCGGCCGAGGCCTCCCGCCCCAGTA.CTTGCTGGCAGGGAT 52
          || || | || | | || | | | || | | | || | |
151 TTCTCCTTCGGGTCCGGGACTCTGGGCTCCACCACCGTGGCCGCCGGCGG 200
          53 TAAGAGCAGA.TAAAAGTGTGCTCACACACTGTAGACACGGCTACCATGC 101
          | ||| | | || | | | || | | | || | | |
201 GACCAGCACAGGCGGCGTTTTCTCCTTCGGAACGGGAACGTCTAGCAACC 250
          102 CATC.....CACAGTGTTGCCATCCACAGTGTTGCCATCACTCCTGC. 143
          || | | || | | | || | | | || | | | || | |
251 CTTCTGTGGGGCTCAATTTTGGAAATCTTGAAGTACTTCAACTCCAGCA 300
          144 .CCACAGCAGGAGCT..GGCTGGAGCATGAGGTGGATTCTGTG..CTGGA 188
          | ||| | | || | | | || | | | || | |
301 ACTACATCTGCTCCTTCAAGTGGTTTTGGAACCGGGCTCTTTGGATCTAA 350
```

189 GCCTCACCCCT...CTGCCTGATGGCGCAGACGGCCTTGGGTGCCTTGACAC 235
||| | || | || | || | |||
351 ACCTGCCACTGGGTTCACTCTAGGAGGA.ACAAATACAGGTGCCTTGACAC 399

236 ACCAAGAGGCCTCAAGTGGTCACCAAATATGGAACCCTGCAAGGAAAACA 285
|||||
400 ACCAAGAGGCCTCAAGTGGTCACCAAATATGGAACCCTGCAAGGAAAACA 449

286 GATGCATGTGGGGAAGACACCCATCCAAGTCTTTTTTAGGAGTCCCCTTCT 335
|||||
450 GATGCATGTGGGGAAGACACCCATCCAAGTCTTTTTTAGGAGTCCCCTTCT 499

336 CCAGACCTCCTCTAGGTATCCTCAGGTTTGCACCTCCAGAACCCCCGGAG 385
|||||
500 CCAGACCTCCTCTAGGTATCCTCAGGTTTGCACCTCCAGAACCCCCGGAG 549

386 CCCTGGAAAGGAATCAGAGATGCTACCACCTACCCGCCTG..... 425
|||||
550 CCCTGGAAAGGAATCAGAGATGCTACCACCTACCCGCCTGGATGGAGTCT 599

426GGTGCCTGCAGGAGTCCTGGGGCCAGCTGGCCTCGATGTA 465
|||||
700 TGGGGCTACAGGTGCCTGCAGGAGTCCTGGGGCCAGCTGGCCTCGATGTA 749

466 CGTCAGCACGCGGGAACGGTACAAGTGGCTGCGCTTCAGCGAGGACTGTC 515
|||||
750 CGTCAGCACGCGGGAACGGTACAAGTGGCTGCGCTTCAGCGAGGACTGTC 799

516 TGTACCTGAACGTGTACGCGCCGGCGCGCGCGCCCGGGGATCCCCAGCTG 565
|||||
800 TGTACCTGAACGTGTACGCGCCGGCGCGCGCGCCCGGGGATCCCCAGCTG 849

566 CCAGTGATGGTCTGGTTCCCGGGAGGCGCCTTCATCGTGGGCGCTGCTTC 615
|||||
850 CCAGTGATGGTCTGGTTCCCGGGAGGCGCCTTCATCGTGGGCGCTGCTTC 899

616 TTCGTACGAGGGCTCTGACTTGGCCGCCCGCGAGAAAGTGGTGCTGGTGT 665
|||||
900 TTCGTACGAGGGCTCTGACTTGGCCGCCCGCGAGAAAGTGGTGCTGGTGT 949

666 TTCTGCAGCACAGGCTCGGCATCTTCGGCTTCCTGAGCACGGACGACAGC 715
|||||
950 TTCTGCAGCACAGGCTCGGCATCTTCGGCTTCCTGAGCACGGACGACAGC 999

716 CACGCGCGCGGGAACCTGGGGGCTGCTGGACCAGATGGCGGCTCTGCGCTG 765



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FIG. 3C ~~FIG. 4C~~

766 GGTGCAGGAGAACATCGCAGCCTTCGGGGGAGACCCAGGAAATGTGACCC 815
|||||
1050 GGTGCAGGAGAACATCGCAGCCTTCGGGGGAGACCCAGGAAATGTGACCC 1099

816 TGTTCGGCCAGTCGGCGGGGGCCATGAGCATCTCAGGACTGATGATGTCA 865
|||||
1100 TGTTCGGCCAGTCGGCGGGGGCCATGAGCATCTCAGGACTGATGATGTCA 1149

866 CCCCTAGCCTCGGGTCTCTTCCATCGGGCCATTTCCCAGAGTGGCACCGC 915
|||||
1150 CCCCTAGCCTCGGGTCTCTTCCATCGGGCCATTTCCCAGAGTGGCACCGC 1199

916 GTTATTTCAGACTTTTCATCACTAGTAACCCACTGAAAGTGGCCAAGAAGG 965
|||||
1200 GTTATTTCAGACTTTTCATCACTAGTAACCCACTGAAAGTGGCCAAGAAGG 1249

966 TTGCCCACCTGGCTGGATGCAACCACAACAGCACACAGATCCTGGTAAAC 1015
|||||
1250 TTGCCCACCTGGCTGGATGCAACCACAACAGCACACAGATCCTGGTAAAC 1299

1016 TGCCTGAGGGCACTATCAGGGACCAAGGTGATGCGTGTGTCCAACAAGAT 1065
|||||
1300 TGCCTGAGGGCACTATCAGGGACCAAGGTGATGCGTGTGTCCAACAAGAT 1349

1066 GAGATTCCTCCAAGTGAAGTTCAGAGAGACCCGGAAGAGATTATCTGGT 1115
|||||
1350 GAGATTCCTCCAAGTGAAGTTCAGAGAGACCCGGAAGAGATTATCTGGT 1399

1116 CCATGAGCCCTGTGGTGGATGGTGTGGTGATCCCAGATGACCCTTTGGTG 1165
|||||
1400 CCATGAGCCCTGTGGTGGATGGTGTGGTGATCCCAGATGACCCTTTGGTG 1449

1166 CTCCTGACCCAGGGGAAGGTTTCATCTGTGCCCTACCTTCTAGGTGTCAA 1215
|||||
1450 CTCCTGACCCAGGGGAAGGTTTCATCTGTGCCCTACCTTCTAGGTGTCAA 1499

1216 CAACCTGGAATTCAATTGGCTCTTGCTTATATCATGAAGTTCCCGCTAA 1265
|||||
1500 CAACCTGGAATTCAATTGGCTCTTGCTTAT..... 1530

.
.

1316 CGCACCCTGTTGAATATCACCAAGGAGCAGGTACCACTTGTGGTGGAGGA 1365
|||||
1531AATATCACCAAGGAGCAGGTACCACTTGTGGTCGAGGA 1568

1366 GTACCTGGACAATGTCAATGAGCATGACTGGAAGATGCTACGAAACCGTA 1415



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FIG. 3D ~~FIG. 4D~~

1416 TGATGGACATAGTTCAAGATGCCACTTTCGTGTATGCCACACTGCAGACT 1465
|||||
1619 TGATGGACATAGTTCAAGATGCCACTTTCGTGTATGCCACACTGCAGACT 1668
1466 GCTCACTACCACCGAGATGCCGGCCTCCCTGTCTACCTGTATGAATTTGA 1515
|||||
1669 GCTCACTACCACCGA..... 1683
.
.
.
1666 CAACTTTGCCCCGCACAGGAAACCCCAATGATGGGAATCTGCCCTGCTGGC 1715
|||||
1684GAAACCCCAATGATGGGAATCTGCCCTGCTGGC 1716
1716 CACGCTACAACAAGGATGAAAAGTACCTGCAGCTGGATTTTACCACAAGA 1765
|||||
1717 CACGCTACAACAAGGATGAAAAGTACCTGCAGCTGGATTTTACCACAAGA 1766
1766 GTGGGCATGAAGCTCAAGGAGAAGAAGATGGCTTTTTTGGATGAGTCTGTA 1815
|||||
1767 GTGGGCATGAAGCTCAAGGAGAAGAAGATGGCTTTTTTGGATGAGTCTGTA 1816
1816 CCAGTCTCAAAGACCTGAGAAGCAGAGGCAATTCTAAGGGTGGCTATGCA 1865
|||||
1817 CCAGTCTCAAAGACCTGAGAAGCAGAGGCAATTCTAAGGGTGGCTATGCA 1866
1866 GGAAGGAGCCAAAGAGGGGTTTGCCCCCACCATCCAGGCCCTGGGGAGAC 1915
|||||
1867 GGAAGGAGCCAAAGAGGGGTTTGCCCCCACCATCCAGGCCCTGGGGAGAC 1916
1916 TAGCCATGGACATACCTGGGGACAAGAGTTCTACCCAAGGGCGAATTCGT 1965
|||||
1917 TAGCCATGGACATACCTGGGGACAAGAGTTCTACCCA...CCCCA...GT 1960
1966 TTAAACCTGCAGGA.CTAG..... 1983
|||
1961 TTAGAACTGCAGGAGCTCCCTGCTGCCTCCAGGCCAAAGCTAGAGCTTTT 2010
.
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FIG. 4B

FIG. 5B

160	170	180	190	200	210
COE-2	VWFP	GAFIVGA	ASSYEGSDLAAREKVVLF	QLQHR	LIGFGLSTDDSHARGNWGLLDQMA
	:	:	:	:	:
pro873	VWFP	GAFIVGA	ASSYEGSDLAAREKVVLF	QLQHR	LIGFGLSTDDSHARGNWGLLDQMA
	250	260	270	280	290 300
220	230	240	250	260	270
COE-2	ALRWVQENIAAF	GDPGNVTLFGQ	SAGAMSISGLMMSPLASGLFHRAISQSGTALFRLFI		
	:	:	:	:	:
pro873	ALRWVQENIAAF	GDPGNVTLFGQ	SAGAMSISGLMMSPLASGLFHRAISQSGTALFRLFI		
	310	320	330	340	350 360
280	290	300	310	320	330
COE-2	TSNPLKVAKKVAH	LACGNHNSQILVNC	LALSGTKVMRVS	NKMRFLQ	NFQRPDEEIIW
	:	:	:	:	:
pro873	TSNPLKVAKKVAH	LACGNHNSQILVNC	LALSGTKVMRVS	NKMRFLQ	NFQRPDEEIIW
	370	380	390	400	410 420
340	350	360	370	380	390
COE-2	SMSPVVDG	VVIPDDPLVLLTQ	GKVSSVPYLLGVNNLEFNWLLPYIMKFPLNRQAMRKETI		
	:	:	:	:	:
pro873	SMSPVVDG	VVIPDDPLVLLTQ	GKVSSVPYLLGVNNLEFNWLLPY	-----	
	430	440	450	460	
400	410	420	430	440	450
COE-2	TKMLWSTR	LLNITKEQVPLVVEEYLDNVNEHDWKMLNRNMDIVQDATFFVYATLQTAHY			
	:	:	:	:	:
pro873	-----	NITKEQVPLVVEEYLDNVNEHDWKMLNRNMDIVQDATFFVYATLQTAHY			
	470	480	490	500	510



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FIG. 4C

~~FIG. 5C~~

460 470 480 490 500 510
COE-2 HRDAGLPVLYEFEHARGIIVKPRTDGADHGDENYFLFGGPFATGLSMGKEKALSLQMM
::: : : : :
pro873 HRET--PMM-----GIC--P---AGHA-----
520

520 530 540 550 560 570
COE-2 KYWANFARTGNPNDGNLPCWPRYNKDEKYLQLDFTTRVGMKLEKKMAFWMSLYQSQRPE
::: : : : :
pro873 -----TTRM-----KSTCSWIL-----P-
530 540

580
COE-2 KQRQF
:
pro873 -QEWA



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FIG. 5A

FIG. 6A

90
80
70
60
50
40
30
20
10
0



	Adrenal Gland	Brain	Heart	Kidney	Liver	Lung	Mammary Gland	Placenta	Prostate	Salivary Gland
18903 MEAN	25.93	23.86	27.95	25.64	25.24	25.41	24.36	26.50	25.73	24.55
β2M803 MEAN	18.73	20.22	18.66	18.06	19.06	16.89	17.47	18.06	17.90	18.74
ΔCt	7.20	3.64	9.29	7.58	6.18	8.52	6.89	8.45	7.83	5.81
Expression	6.80	80.49	1.60	5.23	13.79	2.72	8.43	2.87	4.39	17.82



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FIG. 5B

FIG. 6B

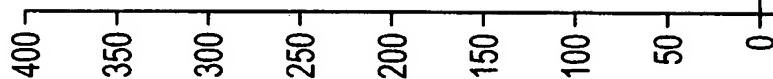
Muscle	Sm. Intestine	Spleen	Stomach	Teste	Thymus	Trachea	Uterus	Spinal Cord	Skin	DRG
29.70	25.43	26.89	26.27	24.29	26.33	25.14	26.18	23.99	23.01	25.06
20.66	17.86	16.37	18.03	19.32	18.19	19.10	18.53	19.20	17.10	19.07
9.04	7.58	10.52	8.25	4.97	8.15	6.04	7.66	4.80	5.91	5.99
1.91	5.24	0.68	3.30	31.91	3.53	15.25	4.96	36.02	16.63	15.73



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FIG. 6A

FIG. 7A



	MK cortex	MK DRG	MK spinal cord	MK sciatic nerve	MK kidney	MK hairy skin	MK heart LV	MK gastro muscle	MK liver
18903 Average Ct	36.935	40	35.89	40	33.735	36.89	37.44	37.235	27.39
HK Average Ct	20.365	17.375	18.71	17.37	17.78	18.295	17.655	18.91	18.22
delta Ct	16.57	22.625	17.18	22.63	15.955	18.595	19.785	18.325	9.17
Relative Expression	0.01579689	0.00023759	0.01035007	0.00023677	0.02419385	0.00388138	0.00170122	0.0046802	2.66804738






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FIG. 6B

FIG. 7B



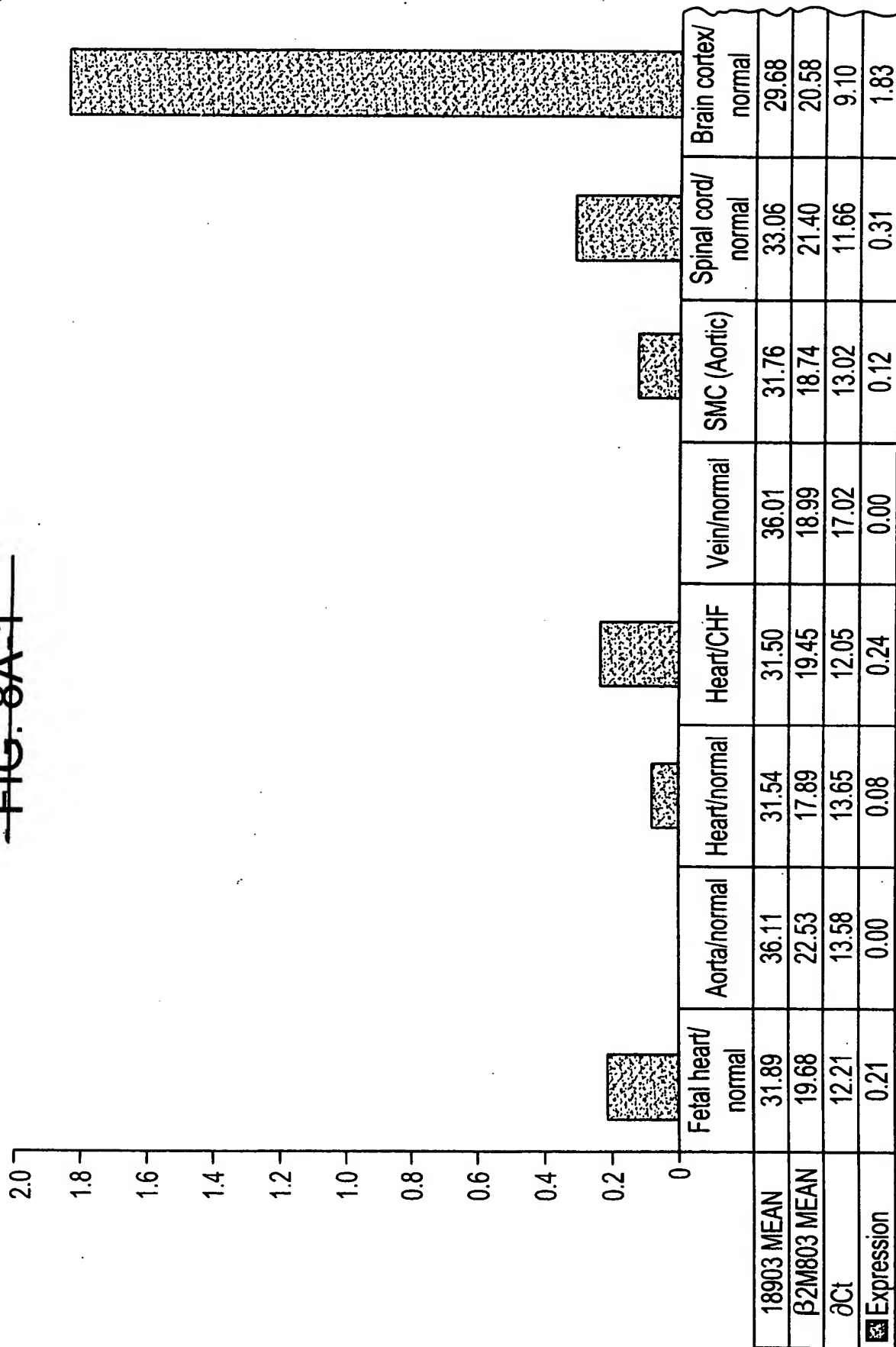
					
	Hu. Brain	Hu. Spinal cord	Hu. Heart	Hu. Kidney	Hu. Liver
	Hu. Lung				
	Hu. Lung	Hu. Liver	Hu. Kidney	Hu. Heart	Hu. Brain
	21.27	23.78	28.26	26.155	25.43
	19.245	18.295	17.855	17.925	18.22
	2.025	5.485	10.405	8.23	7.21
	377.618146	34.3154004	1.13349992	5.11872423	10.3803579
					1.57002147



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FIG. 7A-1

FIG. 8A-1





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FIG. 7A-2
~~FIG. 8A-2~~

	Brain hypothalamus	Glioma cells (Astrocytes)	Brain/ Glioblastoma	Breast/ normal	Breast tumor/ IDC	OVARY/ Normal	OVARY/ Tumor	Pancreas	Prostate/ Normal	Prostate/ Tumor
	29.45	33.94	30.39	30.10	30.75	31.73	33.59	30.88	31.16	29.03
	19.24	21.09	17.43	18.60	17.66	19.95	18.91	17.33	18.34	17.57
	10.21	12.86	12.97	11.50	13.09	11.79	14.68	13.55	12.83	11.46
	0.85	0.13	0.13	0.35	0.11	0.28	0.04	0.08	0.14	0.35



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FIG. 7A-3

FIG. 8A-3

Colon/normal	Colon/tumor	Colon/IBD	Kidney/ normal	Liver/normal	Liver fibrosis	Fetal Liver/ normal	Lung/normal	Lung/tumor
32.03	30.80	32.37	30.98	31.82	30.10	33.55	30.54	30.30
17.78	18.15	17.72	20.03	19.08	18.82	21.39	17.31	17.77
14.26	12.66	14.65	10.95	12.75	11.29	12.16	13.23	12.53
0.05	0.16	0.04	0.51	0.15	0.40	0.22	0.10	0.17



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FIG. 7A-4

~~FIG. 8A-4~~

Lung/COPD	Tonsil/normal	Lymph node/ normal	Thymus/ normal	Epithelial Cells (Prostate)	Endothelial Cells (Aortic)	Skeletal Muscle	Fibroblasts (Dermal)	Skin/Normal	Adipose/ Normal
29.44	31.13	31.40	32.80	30.70	35.27	31.06	33.10	31.16	32.43
17.10	17.19	17.91	20.03	20.13	20.16	18.26	18.18	20.29	17.96
12.34	13.94	13.49	12.78	10.57	15.11	12.81	14.92	10.87	14.47
0.19	0.06	0.09	0.14	0.66	0.03	0.14	0.03	0.54	0.04

FIG. 7A-5

~~FIG. 8A-5~~

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Osteoblasts (Primary)	Osteoblasts (Undiff)	Osteoblasts (Diff)	Osteoclasts	Aorta SMC (Early)	Aorta SMC (Late)	HUVEC	HMVEC
34.84	33.19	33.23	32.47	32.50	32.72	32.17	32.74
20.44	18.50	17.83	17.25	19.53	18.77	19.27	18.74
14.40	14.69	15.40	15.22	12.97	13.96	12.91	14.00
0.05	0.04	0.02	0.03	0.13	0.06	0.13	0.06





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FIG. 7B

FIG. 8B

Tissue	18903 MEAN	β 2M803 MEAN	δ Ct	Expression
Fetal heart/normal	31.89	19.68	12.21	0.21
Aorta/normal	36.11	22.53	13.58	0.00
Heart normal	31.54	17.89	13.65	0.08
Heart/CHF	31.50	19.45	12.05	0.24
Vein/normal	36.01	18.99	17.02	0.00
SMC (Aortic)	31.76	18.74	13.02	0.12
Spinal cord/normal	33.06	21.40	11.66	0.31
Brain cortex/normal	29.68	20.58	9.10	1.83
Brain hypothalamus/normal	29.45	19.24	10.21	0.85
Glial cells (Astrocytes)	33.94	21.09	12.86	0.13
Brain/Glioblastoma	30.39	17.43	12.97	0.13
Breast/normal	30.10	18.60	11.50	0.35
Breast tumor/IDC	30.75	17.66	13.09	0.11
Ovary/normal	31.73	19.95	11.79	0.28
Ovary/tumor	33.59	18.91	14.68	0.04
Pancreas	30.88	17.33	13.55	0.08
Prostate/normal	31.16	18.34	12.83	0.14
Prostate/tumor	29.03	17.57	11.46	0.35
Colon/normal	32.03	17.78	14.26	0.05
Colon/tumor	30.80	18.15	12.66	0.16
Colon/IBD	32.37	17.72	14.65	0.04
Kidney/normal	30.98	20.03	10.95	0.51
Liver/normal	31.82	19.08	12.75	0.15
Liver/fibrosis	30.10	18.82	11.29	0.40
Fetal Liver/normal	33.55	21.39	12.16	0.22
Lung/normal	30.54	17.31	13.23	0.10
Lung/tumor	30.30	17.77	12.53	0.17
Lung/COPD	29.44	17.10	12.34	0.19
Tonsil/normal	31.13	17.19	13.94	0.06
Lymph node/normal	31.40	17.91	13.49	0.09
Thymus/normal	32.80	20.03	12.78	0.14
Epithelial Cells(prostate)	30.70	20.13	10.57	0.66
Endothelial Cells(aortic)	35.27	20.16	15.11	0.03
Skeletal Muscle/normal	31.06	18.26	12.81	0.14
Fibroblasts (Dermal)	33.10	18.18	14.92	0.03
Skin/normal	31.16	20.29	10.87	0.54
Adipose/normal	32.43	17.96	14.47	0.04
Osteoblasts (primary)	34.84	20.44	14.40	0.05
Osteoblasts (Undiff)	33.19	18.50	14.69	0.04
Osteoblasts (Diff)	33.23	17.83	15.40	0.02
Osteoblasts	32.47	17.25	15.22	0.03
Aorta SMC (Early)	32.50	19.53	12.97	0.13
Aorta SMC (Late)	32.72	18.77	13.96	0.06
HUVEC	32.17	19.27	12.91	0.13
HMVEC	32.74	18.74	14.00	0.06
	40.00	40.00	0.00	